
Registration, Orientation, and Similarity of Molecular Electrostatic Potentials through Multipole Matching

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ABSTRACT

The use of a multipolar decomposition of the far electrostatic potential for the purposes of molecular field similarity comparison between structurally different molecules has been impractical because the multipolar decomposition depends on the center of expansion. That center of expansion is essentially arbitrary, which renders the multipolar coefficients to be a nonunique characterization of the field. This article provides the definition of a center of expansion at which the multipolar decomposition is unique. For the first time, it is possible to use multipolar decomposition to characterize molecular fields beyond the first term, which is invariant under translation of the center of expansion. Calculations are performed for two structurally distinct types of HIV-1 inhibitors, three non-nucleoside reverse transcriptase inhibitors, and three phospholipids using these unique multipolar descriptors. Differences and similarities in the calculated values of these descriptors will be shown to parallel the differences and similarities of molecular charge distributions. © 1996 by John Wiley & Sons, Inc.

Introduction

Electrostatic interactions at the molecular level contribute to important determinants of biological activity. In rational drug design, one of the important descriptors utilized in 3D Quantitative Structure Activity Relations (QSAR) and, more specifically, Comparative Molecular Field Analysis (CoMFA)¹ is the electrostatic potential over an extensive region of space in the vicinity of the

molecules whose pharmacological properties are under investigation. Comparison of electrostatic potentials is generally accomplished by registering the structures,¹ steric features,² or electrostatic potentials³ to achieve maximum overlap with respect to the relative translation and rotation of the different molecules. Electrostatic interactions at distances greater than those of consequence for chemical reactivity are also of interest. For example, cytochrome oxidase and reductase, both electrostatically negative, are directed to the active heme crevice of cytochrome *c* by the positively charged lysine residues that are clustered around

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the crevice. The quantitative characterization of the electrostatic field is useful for studying a wide range of problems, from the conservation of electrostatic features of important biomolecules across species to the quantitative characterization of active drug molecules.

In this article we describe a simple and, for the first time, a unique quantitative characterization of the electrostatic potential with use of an electrostatic multipolar decomposition. One prime motivation in developing such decomposition is to provide the capability for rapid comparison of symmetry-related features of the electrostatic fields of different molecules without the limitations imposed by requiring spatial alignment via translation or rotation of the fields or potentials of these molecules.

The lowest nonvanishing order of a multipolar expansion is defined by a moment that is a constant under translation of the center of expansion. Multipole moments of order higher than the lowest nonvanishing order are a function of the spatial location of the origin of expansion. For a molecule with zero net charge, the dipole is invariant with respect to the choice of origin of expansion whereas the quadrupole and all higher order moments depend on the choice of this origin. Dipole moments of different neutral molecules can then be readily compared whereas such comparison among the higher-order multipole moments is not possible unless some special origin of multipole expansion can be defined. The objective of this article is to define just such an origin so that a comparison can be made among the quadrupole moments of a set of structurally and electronically diverse molecules.

The quadrupolar tensor is the tensor of lowest-order rank that provides a unique orthogonal set of axes in three-dimensional space, orienting the electrostatic field to quadrupolar order. These axes, together with the uniquely defined origin of expansion, can then be utilized as a Cartesian reference frame for additional structural features of a molecule (e.g., local reactive sites). In this manner, the local descriptive features of a molecule can then be simply tied together with the more global far electrostatic potential profile of the molecule. Such coordination and compaction of information is expected to be useful in addressing massive amounts of molecular structural and electronic data.

The centers of expansion utilized for molecular species with different lowest nonvanishing orders of multipole expansion will be the different "centers of moment" formally alluded to previ-

ously.⁴ The choice of such centers is dictated by the constraints that they impose on the convergence of the leading terms in the multipolar series expansion of the electrostatic potential. In this article a general definition of the center of N -pole will be given and formulas will be derived for the various centers of moment (i.e., centers of monopole, dipole, quadrupole, etc.). This article also presents calculations performed on several HIV-1 inhibitors. The differences and similarities in the values obtained for the dipolar and quadrupolar descriptors will be shown to parallel the differences and similarities of the molecular charge distributions. Finally, this article summarizes key points and suggests future applications of potential interest and importance.

Center of N -Pole

The multipolar expansion provides an immediate characterization of the geometric organization of the field as a function of the moments of the charge distribution.⁵ The objective of this section is to define a center of N -pole for an arbitrary set of molecules with vanishing multipole moments up to but not including order N that would define or register a center of expansion for each molecule, rendering the multipolar expansion unique to within an arbitrary rotation.

A natural sense of a center would be one in which the leading term would be dominant throughout most of space. Since the higher orders fall off as powers of $1/r$, it follows that most of space will be characterized by the leading terms only. The way to ensure that the leading term most effectively dominates most of space is to find the center where the contributions from the next to leading term are, in some sense, as small as possible. In the case of center of charge, this is easily achieved at the point where the dipole is simply zero. The definition of *center of dipole* and higher-order moments is more involved. As pointed out previously,⁴ all quadrupolar components vanish for a molecule such as HF at the center of dipole. This is actually a consequence of the cylindrical symmetry about the linear molecular axis. For general molecular symmetry or asymmetry, however, all five independent quadrupolar components cannot be made to vanish by an arbitrary translation of the origin of multipolar expansion. One requires, therefore, a criterion to define what is meant by the center of dipole for the case of general molecular asymmetry.

A measure of the residue of deviation from the leading term at any center of expansion, dependent only on r and independent of angle, can be defined. Such a measure may be obtained by evaluating $\oint d\Omega |\phi - \phi_N|^2$, where $d\Omega$ is the element of solid angle, ϕ is the electrostatic potential, and ϕ_N is the contribution to the potential from the leading N -pole term. The orthogonality of the multipoles isolates the contribution from each order. The leading term of the residue dominates the largest volume of space. The general center of N -pole is determined by minimizing the leading term of this residue with respect to the center of expansion.

If the molecule is charged, the leading term is the monopole term. The location in space where the next order contributes a minimum is the center of monopole. Minimizing the contribution to $\oint d\Omega |\phi - \phi_0|^2$ from the leading dipolar term with respect to the translation of the center of expansion leads to the condition that at this center the dipole is zero. The center of monopole is then just the familiar center of charge. The orientation and magnitude information contained in the two leading nonzero terms will then be the total charge, the two independent principal values of the quadrupole tensor (the quadrupole tensor is traceless), and the three principal axes. The choice of center of monopole as the origin of expansion also guarantees that the monopolar contribution to the electrostatic potential most closely approximates the total electrostatic potential over most of space. Thus, the familiar center of charge has meaning within the more general context of the present discussion by being the center of monopole.

For arbitrary origin of multipolar expansion for neutral polar molecules, multipolar comparison begins at the dipolar level of the expansion. Determination of a center of dipole will allow a simple and straightforward comparison of moments up to the quadrupolar level of approximation.

The criterion that defines the center of dipole yields a relationship between dipolar orientation and principal quadrupolar axes that is invariant with respect to molecular structure and distribution of charge. Minimization of the next to leading term in the series contributing to $\oint d\Omega |\phi - \phi_1|^2$ leads to the condition that $\mathbf{Q} \cdot \vec{p} = \vec{0}$, where \mathbf{Q} is the quadrupole tensor and \vec{p} is the dipole moment. This implies that the dipolar direction lies along one of the principal axes of the quadrupole and that the quadrupolar principal value associated with that direction is zero. Information con-

tained in the first two nonvanishing moments is therefore the magnitude of the dipole, one quadrupole moment (again, the quadrupole tensor is traceless, with one principal value equal to zero in this case), and the orthogonal principal axes (the dipole direction is one of those axes). Furthermore, the quadrupolar tensor of each molecule yields an orthogonal set of principal axes in three-dimensional space that can be utilized as a Cartesian reference frame for other molecular features of importance.

For the case of a neutral nonpolar molecule, the leading term is the quadrupole. This tensor will then be invariant under a translation of the center of expansion. However, the point where it will best approximate the electrostatic field over most of space is where the contribution of the leading octopolar term to $\oint d\Omega |\phi - \phi_2|^2$ is a minimum. The quadrupole moment at this point (as well as all others) is characterized by the two independent quadrupolar principal values and the principal axes defined by three numbers. Here again, as the origin of expansion is translated, the choice of the center of quadrupole as the origin of expansion also guarantees that the solid angle average of the leading term quadrupolar contribution to the square of the far field potential most closely approximates the solid angle average of the square of the total electrostatic potential over all of far field space. For this case one need not perform the translation to the center of quadrupole to derive descriptor values up to and including quadrupolar order. One does, however, need the center of quadrupole to obtain the smallest residual contribution to electrostatic potential over far field space above this order.

The electrostatic field satisfies Poisson's equation. Solutions of this equation must be invariant under translation and rotation of the coordinate system utilized. In this case the invariance is expressed in terms of the solution

$$\phi(\vec{x}) = \frac{1}{4\pi\epsilon_0} \int d^3x' \frac{\rho(\vec{x}')}{|\vec{x} - \vec{x}'|} \quad (1)$$

A translational transformation must satisfy

$$\begin{aligned} \vec{\xi} &= \vec{x} - \vec{x}_0, \\ \rho'(\vec{\xi}) &= \rho(\vec{\xi} + \vec{x}_0), \\ \phi'(\vec{\xi}) &= \phi(\vec{\xi} + \vec{x}_0) \end{aligned} \quad (2)$$

for which

$$\phi'(\vec{\xi}) = \frac{1}{4\pi\epsilon_0} \int d^3\xi' \frac{\rho'(\vec{\xi}')}{|\vec{\xi} - \vec{\xi}'|} \quad (3)$$

Equality holds since

$$|\vec{\xi} - \vec{\xi}'| = |(\vec{x} - \vec{x}_0) - (\vec{x}' - \vec{x}_0)| = |\vec{x} - \vec{x}'|$$

The same holds for rotational transformations

$$\begin{aligned} \vec{\xi} &= \mathbf{R} \cdot \vec{x}, \\ d^3\xi &= J \left(\frac{\partial \vec{\xi}}{\partial \vec{x}} \right) d^3x = d^3x \\ \rho'(\vec{\xi}) &= \rho(\mathbf{R} \cdot \vec{x}), \\ \phi'(\vec{\xi}) &= \phi(\mathbf{R} \cdot \vec{x}) \end{aligned} \quad (4)$$

since

$$\begin{aligned} |\vec{\xi} - \vec{\xi}'| &= |\mathbf{R} \cdot \vec{x} - \mathbf{R} \cdot \vec{x}'| \\ &= |\mathbf{R} \cdot (\vec{x} - \vec{x}')| = |\vec{x} - \vec{x}'| \end{aligned}$$

Compositions of rotation and translation of the coordinate axes leave the solutions invariant.

The kernel $1/|\vec{x} - \vec{x}'|$ may be expanded to yield

$$\begin{aligned} \phi(\vec{x}) &= \frac{1}{4\pi\epsilon_0} \sum_j \int d^3x' \rho(\vec{x}') \frac{1}{j!} (-\vec{x}' \cdot \vec{\nabla})^j \frac{1}{|\vec{x}|} \\ &= \frac{1}{4\pi\epsilon_0} \left\{ \int d^3x' \rho(\vec{x}') \frac{1}{|\vec{x}|} \right. \\ &\quad + \int d^3x' \rho(\vec{x}') \frac{\vec{x}' \cdot \hat{x}}{|\vec{x}|^2} \\ &\quad + \frac{1}{2} \int d^3x' \rho(\vec{x}') \\ &\quad \times \frac{3\hat{x} \cdot \vec{x}' \vec{x}' \cdot \hat{x} - |\vec{x}'|^2}{|\vec{x}|^3} + \dots \left. \right\} \end{aligned}$$

Defining

$$\begin{aligned} q &= \int d^3x \rho(\vec{x}), \\ \vec{p} &= \int d^3x \vec{x} \rho(\vec{x}), \\ \mathbf{Q} &= \frac{1}{2} \int d^3x (3\vec{x}\vec{x} - |\vec{x}|^2 \mathbf{1}) \rho(\vec{x}), \\ Q_{ijk} &= \int d^3x [15x_i x_j x_k \\ &\quad - 3r^2(x_i \delta_{jk} + x_j \delta_{ki} + x_k \delta_{ij})] \end{aligned} \quad (5)$$

The form of \mathbf{Q} conforms to the usage of Jackson,⁵ which differs from Buckingham⁴ by a factor of 2. The expansion becomes

$$\begin{aligned} \phi(\vec{x}) &= \frac{1}{4\pi\epsilon_0} \frac{q}{|\vec{x}|} + \frac{1}{4\pi\epsilon_0} \frac{\vec{p} \cdot \hat{x}}{|\vec{x}|^2} + \frac{1}{4\pi\epsilon_0} \frac{\hat{x} \cdot \mathbf{Q} \cdot \hat{x}}{|\vec{x}|^3} \\ &\quad + \frac{1}{4\pi\epsilon_0} \frac{Q_{ijk} \hat{x}_i \hat{x}_j \hat{x}_k}{6|\vec{x}|^4} + \dots \end{aligned} \quad (6)$$

The contribution at \vec{x}' from $1/|\vec{x} - \vec{x}'|$ is collapsed to a series in $1/|\vec{x}|^j$ at $\vec{x}' = \vec{0}$. That series then accumulates contributions from all the $\rho(\vec{x}')$ at $\vec{0}$. The contributions from each of the orders in the expansion show up as moments called multipoles. The first order, q , is called the monopole moment; the second, \vec{p} , is called the dipole moment; \mathbf{Q} is called the quadrupole moment, etc.

Under translation, the expansion should have the same form. Namely,

$$\begin{aligned} \phi'(\vec{\xi}) &= \frac{1}{4\pi\epsilon_0} \frac{q'}{|\vec{\xi}|} + \frac{1}{4\pi\epsilon_0} \frac{\vec{p}' \cdot \hat{\xi}}{|\vec{\xi}|^2} \\ &\quad + \frac{1}{4\pi\epsilon_0} \frac{\hat{\xi} \cdot \mathbf{Q}' \cdot \hat{\xi}}{|\vec{\xi}|^3} \\ &\quad + \frac{1}{4\pi\epsilon_0} \frac{Q'_{ijk} \hat{\xi}_i \hat{\xi}_j \hat{\xi}_k}{6|\vec{\xi}|^4} + \dots \end{aligned} \quad (7)$$

Under translation, the values of q' , \vec{p}' , \mathbf{Q}' , and Q'_{ijk} must be related to q , \vec{p} , \mathbf{Q} , and Q_{ijk} so that $\phi'(\vec{\xi}) = \phi(\vec{x})$. Further, the relationship to the expansion of $1/|\vec{x} - \vec{x}_0|$ must be preserved in the definitions of the multipole moments. The transformations that achieve this are

$$\begin{aligned} q' &= q, \\ \vec{p}' &= \vec{p} - q\vec{x}_0, \\ 2\mathbf{Q}' &= 2\mathbf{Q} - (3\vec{x}_0 \vec{p} + 3\vec{p} \vec{x}_0 - 2\vec{x}_0 \cdot \vec{p} \mathbf{1}) \\ &\quad + q(3\vec{x}_0 \vec{x}_0 - |\vec{x}_0|^2 \mathbf{1}), \\ Q'_{ijk} &= Q_{ijk} + 10Q_{jk} x_{0i} + 10Q_{ki} x_{0j} + 10Q_{ij} x_{0k} \\ &\quad - 4Q_{il} \delta_{jk} x_{0l} - 4Q_{jl} \delta_{ki} x_{0l} - 4Q_{kl} \delta_{ij} x_{0l} \\ &\quad - 6(x_{0i} \delta_{jk} + x_{0j} \delta_{ki} + x_{0k} \delta_{ij}) \vec{x}_0 \cdot \vec{p} \\ &\quad + 15q x_{0i} x_{0j} x_{0k} \\ &\quad - 3q \vec{x}_0 \cdot \vec{x}_0 (x_{0i} \delta_{jk} + x_{0j} \delta_{ki} + x_{0k} \delta_{ij}) \end{aligned} \quad (8)$$

This can be extended to higher-order terms.

Without a way to specify an origin that depends entirely on the characteristics of the charge distribution, there is no unique multipole expansion since the center is essentially arbitrary. This renders the moments useless for comparative purposes.

When the origin of multipolar expansion is displaced, corrections to the higher-order multipolar terms arise from linear combinations of lower-order terms whose coefficients are polynomials in the displacement. A single monopole displaced from its origin of expansion will generate an infinite number of higher-order multipolar corrections to the electrostatic multipolar expansion. The monopole contributes only one term to the multipolar expansion of the electrostatic potential when monopolar location and origin of expansion coincide. Given a distributed net charge, there is a point where the leading term is the dominant contributor. If the net charge is zero, the leading term might be a dipole. Then there would be one point where the dipole would be the dominant contributor to the series. A way to characterize the contribution of the multipole terms in the series

$$\begin{aligned}\phi(\vec{x}) &= \sum_{l=N}^{\infty} \phi_l(\vec{x}) \\ &= \sum_{l=N}^{\infty} \frac{4\pi}{(2l+1)r^{l+1}} \sum_{m=-l}^l q_{lm} Y_{lm}(\theta, \phi)\end{aligned}$$

is to examine the solid-angle total square residue beyond the leading term

$$\begin{aligned}\oint d\Omega |\phi(\vec{x}) - \phi_N(\vec{x})|^2 \\ = \sum_{l=N+1}^{\infty} \left(\frac{4\pi}{(2l+1)r^{l+1}} \right)^2 \sum_{m=-l}^l |q_{lm}|^2\end{aligned}$$

In this case the magnitude of the contribution from the $1/r^{2l+2}$ th orders may be described by simple rotational invariants. It is possible then to isolate the contributions due to the mixing between orders of the multipole expansion that emerges from the translation transformations. From the preceding, the general idea is to try to define a center to be the place where the total square residue from this mixing will be minimized. Thus the center may be taken to be where $\sum_{m=-l}^l |q_{lm}|^2$ minimizes for $l = N + 1$. So if the leading term is the monopole ($N = 0$), then the contribution from the dipole, $\sum_{m=-1}^1 |q_{1m}|^2$, would be minimized. If the leading contribution were a dipole ($N = 1$),

then the quadrupolar contribution $\sum_{m=-2}^2 |q_{2m}|^2$ is minimized, etc. The point where the monopole is dominant will be called either the center of monopole or center of charge. The point where the leading dipolar contribution would be dominant will be called the center of dipole, and so forth. The term immediately following the leading term falls off as $1/r^2$ with respect to the leading term. Minimizing the contribution to this term will increase convergence most rapidly as r increases.

The relationship between the Cartesian and spherical harmonic expressions for the multipole coefficients involves simple linear combinations.⁵ For the neutral molecule, the quadrupolar contribution involves

$$\sum_m |q_{2m}|^2 = \frac{5}{24\pi} \sum_{ij} |Q_{ij}|^2$$

Also,

$$2\mathbf{Q}' = 2\mathbf{Q} - 3\vec{p}\vec{d} - 3\vec{d}\vec{p} + 2\vec{p} \cdot \vec{d}\mathbf{1}$$

so that

$$2 \frac{\partial Q'_{ij}}{\partial d_k} = -3p_i \delta_{jk} - 3p_j \delta_{ik} + 2p_k \delta_{ij}$$

Thus

$$\frac{\partial}{\partial d_k} \sum_m |q_{2m}|^2 = \frac{-5}{\pi} \sum_i Q'_{ki} p_i$$

The condition for a minimum is then $\mathbf{Q}' \cdot \vec{p} = \vec{0}$. This yields

$$2\mathbf{Q}' \cdot \vec{p} = 2\mathbf{Q} \cdot \vec{p} - \vec{p}(\vec{p} \cdot \vec{d}) - 3p^2 \vec{d} = \vec{0}$$

This may be solved for \vec{d} by first solving for $\vec{p} \cdot \vec{d}$, which may be achieved by dotting the preceding equation with \vec{p} to yield

$$\vec{p} \cdot \vec{d} = \frac{\vec{p} \cdot \mathbf{Q} \cdot \vec{p}}{2p^2}$$

Substituting this into the previous equation and solving for \vec{d} yields

$$\vec{d} = \frac{2}{3p^2} \left[\mathbf{Q} \cdot \vec{p} - \left(\frac{\vec{p} \cdot \mathbf{Q} \cdot \vec{p}}{4p^2} \right) \vec{p} \right]$$

One interesting feature of the center of dipole is that $\mathbf{Q}' \cdot \vec{p} = \vec{0}$. Thus \vec{p} is an eigenvector with

eigenvalue 0. Since $\text{tr} \mathbf{Q} = 0$, it follows that the principal values of the quadrupole tensor are Q , 0, and $-Q$ for some $Q > 0$. Also, since the dipolar direction of \vec{p} lies along one of the quadrupolar principal axes, the two other quadrupolar principal axes are perpendicular to \vec{p} .

Due to symmetry, there are occasions when the dipole is zero in a neutral molecule. In the case of the nonpolar molecule, the quadrupole is the leading term and remains invariant under translation. The point where the octopole is minimized is the point where the quadrupole represents the field the best. Following the aforementioned program, the center of quadrupole is the point where

$$\sum_m |q_{3m}|^2 = \frac{7}{4\pi} \sum_{ijk} |Q_{ijk}|^2$$

is minimized. This occurs when

$$\begin{aligned} \sum_{ij} Q_{ijk} Q_{ij} + 12 \sum_{li} Q_{kii} Q_{il} d_l \\ + 10 \sum_{ij} Q_{ij} Q_{ij} d_l = 0 \end{aligned}$$

which may be solved for \vec{d} . The principal axes of the quadrupole moment are employed. There are now two independent quadrupolar principal values and three principal axes.

Thus the definition of center of N -pole depends entirely on the characteristics of each charge distribution and removes the ambiguity in the multipole moments that limited or excluded their usefulness for the purposes of comparison of electrostatic fields.

Descriptors

The practical merit of using the multipolar comparison as described to address issues related to molecular electrostatic potential similarity will depend on the ability of the lowest-order multipoles to distinguish differences in the symmetry-related features of the charge distribution. Calculations have been performed for two different molecular types of HIV-1 inhibitors. The non-nucleoside reverse transcriptase inhibitors (nnrti's),⁶ TIBO, Nevirapine, and an isoindolinone (Fig. 1) have been chosen since their molecular charge is essentially distributed along the several directions of three-dimensional space. The phospholipids⁷ (Fig. 2), designated as hx1, dd1, and hx2, have been chosen since they are linear molecules having identical polar head groups and dipole moments that arise from a separation of charge essentially along a single direction in space.

The nnrti structures were initially optimized with a TRIPOS⁸ force field calculation followed by an AM1 MOPAC⁹ geometry optimization. The phospholipid structures were optimized solely by a TRIPOS force field calculation. *Ab initio* Gaussian92¹⁰ calculations were then performed on these structures at the 6-31G* Hartree-Fock level of approximation. Final calculations were then performed to obtain the quadrupolar principal values and principal axes orientation at the center of dipole. The results are listed in Table I.

The first three entries for the nnrti's designated as R82150, n96, and iso exhibit moderate dipole moments and large principal quadrupole moments compared with the values of the next three entries

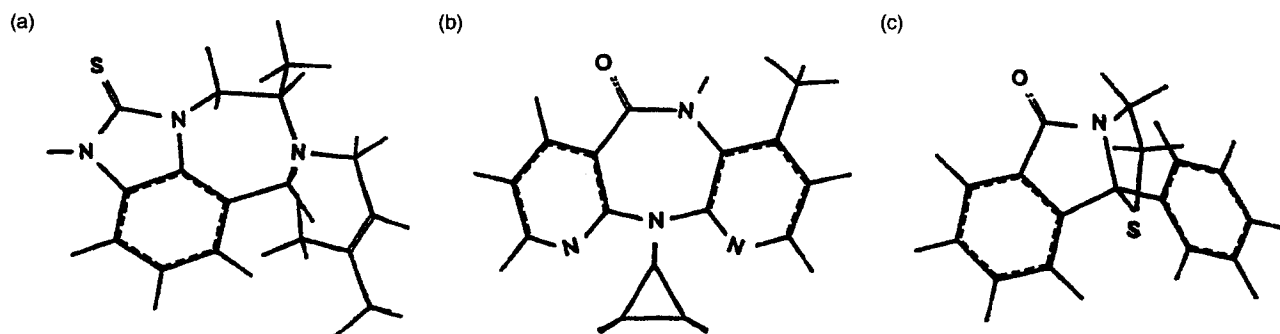


FIGURE 1. Non-nucleoside reverse transcriptase inhibitors (ref. 4). (For all figures, force field and MOPAC calculations have been generated with SYBYL 6.1, available from Tripos Associates Inc., 1669 S. Hanley Rd., St. Louis, MO.) (a) TIBO, (b) Nevirapine, (c) iso (isoindolinone).

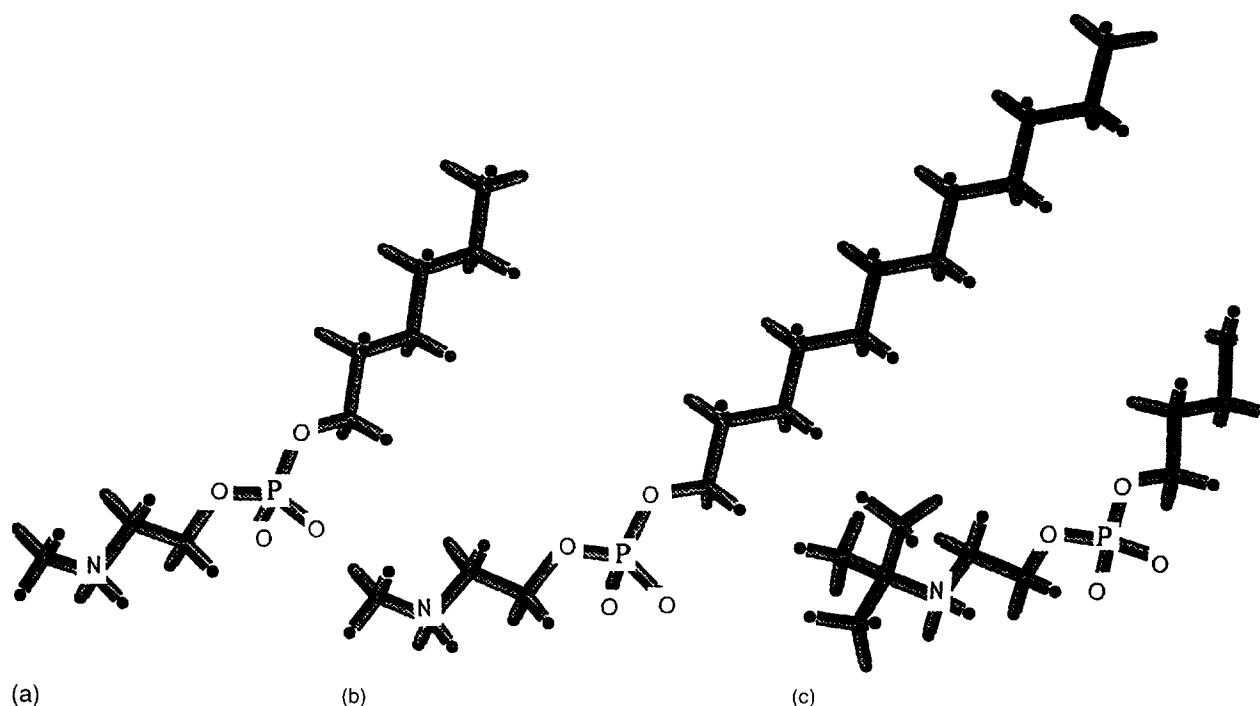


FIGURE 2. Phospholipids (ref. 5). (a) hx1, (b) dd1, (c) hx2.

for the phospholipids, hx1, dd1, and hx2. The phospholipids exhibit large dipole moments with surprisingly small quadrupolar principal values. Such differences between the magnitudes of the quadrupolar values of the two types of molecules highlight spatial differences in their charge distributions.

The relatively large dipole moments of the phospholipids are a consequence of the significant charge separation between the phosphate and amino groups. The relatively small value of the phospholipid principal quadrupole moments arises since most of the contribution to the dipole moment is from charge separation along a single direction in space. Charge separation along this

direction, the net dipolar direction, does not contribute to the magnitude of principal quadrupole moments along this direction. Furthermore, since there is little charge separation in directions perpendicular to this direction (i.e., directions essentially normal to the linear extent of the polar head group of the molecule), the magnitude of the principal quadrupole moment along these directions is relatively small.

The nnrti's exhibit contrasting behavior. They have relatively large quadrupole moments compared with the phospholipids. This is predominantly a consequence of the distributed charge separation in space (i.e., significant charge separation along directions normal to the net dipolar direction).

Figures 3 and 4 illustrate electrostatic potential isosurfaces for the two different types of molecules. These isosurfaces have been generated as follows: First, instead of the extended charge distributions in 6-31G* Gaussian orbitals used to calculate the entries of Table I, Mulliken point charges have been used to simplify the generation of the isosurfaces. The Mulliken point charges at the respective atomic sites have been assigned from calculations performed at the STO-3G level of approximation. Furthermore, each isosurface has been generated about the center of dipole with the dipolar contri-

TABLE I.

Molecule	Dipole (Debye)	Quadrupole (Debye, ^o)
R82150	4.54	13.09
n96	3.15	18.23
iso	2.93	8.79
hx1	23.62	2.11
dd1	23.68	1.19
hx2	24.61	2.38

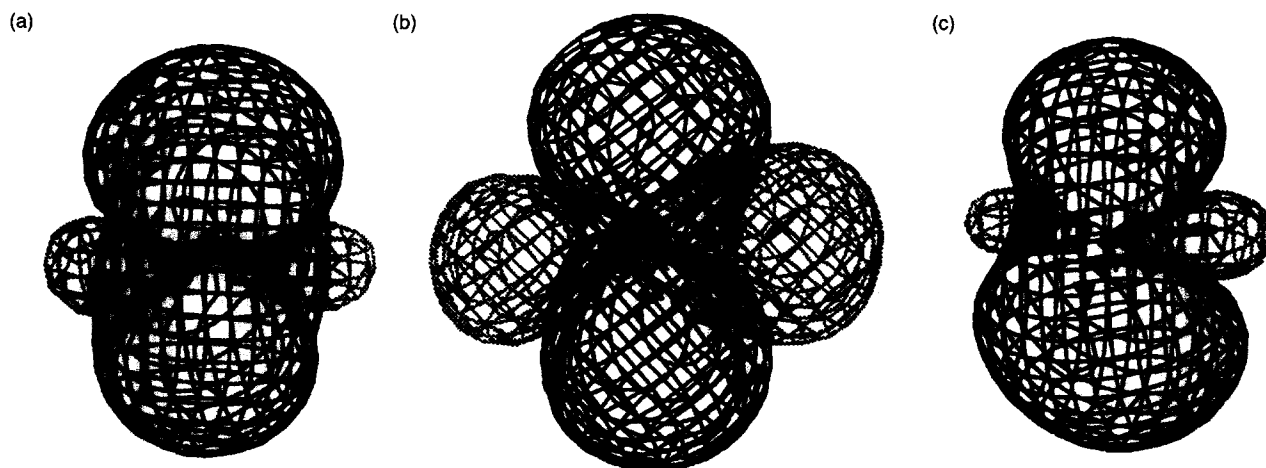


FIGURE 3. Non-nucleoside reverse transcriptase inhibitor isosurfaces (ref. 4). Light gray -0.0003 kcal/mol., dark gray 0.0003 kcal/mol. (a) TIBO, (b) Nevirapine, (c) iso (isoindolinone).

bution to the isosurface subtracted out. Isosurface potential positive and negative values of magnitude 0.0003 kcal/mol have been chosen so that a major portion of the surfaces is in the far field region.

Quadrupolar isosurfaces with one vanishing principal value should look like a four leaf clover. It is of interest that the isosurfaces of the nnrti's (Fig. 3) exhibit such partial character even though the quadrupolar isosurfaces are significantly distorted by contributions from higher-order moments. It is difficult to identify such quadrupolar shapes in connection with the phospholipid isosurfaces. For these molecules the quadrupolar principal values are so small that distortions due to the presence of the higher-order moments mask the four leaf clover shape. The orientations of the nnrti isosurfaces were chosen to highlight four leaf character. For the surfaces shown in Figure 3, one is presumably looking along a direction aligned closely with the net dipolar direction. The line of

sight orientations of the phospholipid isosurfaces were chosen at a slight viewing angle with respect to the dipolar direction. This enhances observation of the positive triple lobe character of the phospholipid isosurfaces. The approximate centers of these lobes lie near a plane containing the dipolar direction.

The ability to subtract the dipolar as well as quadrupolar contributions from the net electrostatic potential calculated about the center of dipole and be left with a residue that can be used for further comparison should enhance the sensitivity of direct methods aimed at achieving electrostatic potential registration between different molecules.

Summary

This article has pointed out that the first two nonvanishing electrostatic multipoles of different

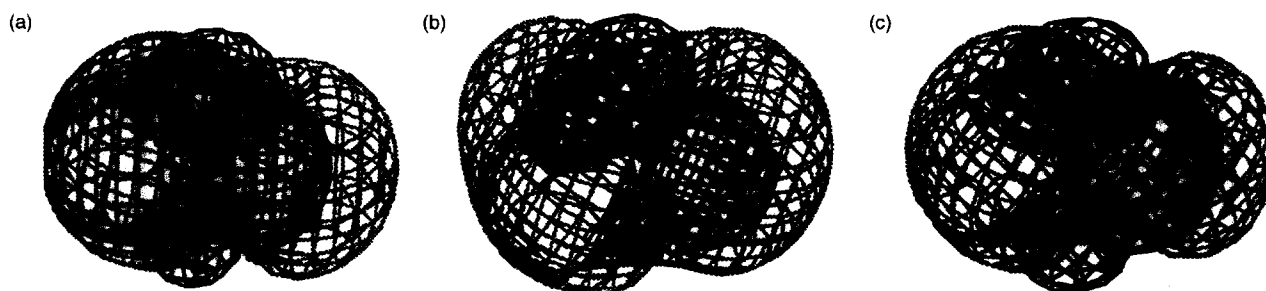


FIGURE 4. Phospholipid isosurfaces (ref. 5). Light gray -0.0003 kcal/mol., dark gray 0.0003 kcal/mol. (a) hx1, (b) dd1, (c) hx2.

molecules can be utilized for purposes of far electrostatic field comparison if the multipolar expansions are performed about the respective centers of N -pole. Such centers have been defined by imposing constraints on the convergence of the first two nonvanishing leading terms of the multipolar series. This ensures that the far field electrostatic potential is most closely approximated by the most slowly varying radially dependent term in the series—namely, the leading term. For two “gedanken” molecules of arbitrary structure but identical charge distribution, the centers so defined would yield moment by moment equality to all orders of expansion.

For ionic species it is possible to find an origin of expansion that yields zero dipole moment, and this leads directly to the center of charge previously utilized in a number of diverse applications.¹¹ For higher-order centers—namely, center of dipole, center of quadrupole, and so forth—it is not generally possible to zero out the second nonvanishing term in the multipolar expansion. For this case an angular averaging procedure has been utilized to enable simple minimization of such a contribution by translation to an appropriate origin of expansion. Imposing such a constraint on the series convergence determines a unique contribution at the quadrupolar level of approximation and hence determines a unique set of axes in three-dimensional space that characterizes the spatial orientation of the electrostatic field up to this level of approximation. This set of axes may be utilized as a reference frame for the coordination of other molecular features. Calculations performed on two very different types of molecules have yielded significant differences in their respective descriptor values and consequently suggest that the pro-

posed procedure in characterizing the far electrostatic fields of different molecules should enable distinctive comparison.

References

1. R. D. Cramer, III, D. E. Patterson, and J. D. Bunce, *J. Am. Chem. Soc.*, **110**, 5959 (1988).
2. A. N. Jain, T. G. Dietterich, R. H. Lathrop, D. Chapman, R. E. Critchlow, Jr., B. E. Bauer, T. A. Webster, and T. Lozano-Perez, *J. Comput.-Aided Molec. Design*, **8**, 635 (1994).
3. C. L. Waller and G. R. Marshall, *J. Med. Chem.*, **36**, 2390 (1993).
4. A. D. Buckingham, In *Advances in Chemical Physics*, **12**, J. O. Hirschfelder, p. 107 (1967).
5. J. D. Jackson, *Classical Electrodynamics*, Wiley, New York, 1975.
6. W. Schafer, W. Friebe, H. Lienert, A. Mertens, T. Poll, W. Von der Saal, H. Zilch, B. Nuber, and M. L. Ziegler, *J. Med. Chem.*, **36**, 726 (1993).
7. D. L. Cooper, K. A. Mort, N. L. Allen, D. Kinchington, and C. McGuigan, *J. Am. Chem. Soc.*, **115**, 12615 (1993).
8. M. Clark, R. D. Cramer, III, and N. Van Opdenbosch, *J. Comp. Chem.*, **10**, 982 (1989).
9. James J. P. Stewart, *J. Comput.-Aided Mol. Design*, **4**, 1 (1990).
10. C. M. J. Frisch, G. W. Trucks, M. Head-Gordon, P. M. W. Gill, M. W. Wong, J. B. Foresman, B. G. Johnson, H. B. Schlegel, M. A. Robb, E. S. Repogle, R. Gomperts, J. L. Andres, K. Raghavachari, J. S. Binkley, C. Gonzales, R. L. Martin, D. J. Fox, D. J. DeFrees, J. Baker, J. J. P. Stewart, and J. A. Pople, Gaussian 92, revision C, Gaussian Inc., Pittsburgh, PA, 1992.
11. (a) Z. Berant, O. Shahal, and Z. Karpas, *J. Phys. Chem.*, **95**, 7534 (1991); (b) G. W. Johnston, H. Kornweitz, I. Schechter, A. Persky, B. Katz, R. Bersohn, and R. D. Levine, *J. Chem. Phys.*, **94**, 2749 (1991); (c) R. M. Herman, *J. Chem. Phys.*, **44**, 1346 (1966); (d) L. Vegh, *Phys. Rev. A*, **37**, 992 (1988); (e) P. Schmelcher and L. S. Cederbaum, *Phys. Rev. A*, **40**, 3515 (1989).